ORNL/FTR--3088

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COVER SHEET
FOR TRIP REPORTS SUBMITTED TO THE OFFICE OF ENERGY RESEARCH

Destination(s) and Dates for Which Trip Report Being Submitted: Amsterdam, The Netherlands (10/3-5/88)
Liege, Belgium (10/6/88)
Bonn, West Germany (10/7-9/88)
Aachen, West Germany (10/9-10/88)

Name of Traveler: Furn F. Knapp, Jr.

Joint Trip Report ☐ Yes
☒ No

If so, Name of Other Traveler(s): _____

OAK RIDGE NATIONAL LABORATORY

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ORNL

FOREIGN TRIP REPORT

ORNL/FTR-3088

DATE: October 27, 1988

SUBJECT: Report of Foreign Travel of F. F. Knapp, Jr., Group Leader, Nuclear Medicine Group, Health and Safety Research Division

TO: Alexander Zucker

FROM: F. F. Knapp, Jr.

PURPOSE: To serve as examiner on doctoral thesis committee in the Cardiology Department, Free University Hospital, Amsterdam, The Netherlands, October 3-5, 1988, and to visit and coordinate collaborative research at the Institute for Clinical and Experimental Nuclear Medicine in Bonn, West Germany, the Department of Nuclear Medicine in Aachen, West Germany, and the Cyclotron Research Center in Liege, Belgium.

SITES VISITED:

10/3-5/88	Cardiology Department Free University Hospital Amsterdam, The Netherlands	J. P. Roos F. Visser
10/6/88	Cyclotron Research Center Liege, Belgium	C. Brihaye
10/7-9/88	Institute for Clinical and Experimental Nuclear Medicine Bonn, West Germany	H.-J. Biersack B. Boelte
10/9/88 10/10/88	Department of Nuclear Medicine University of Aachen Aachen, West Germany	S. N. Reske

ABSTRACT: The traveler was invited to serve as an external examiner for a doctoral thesis entitled "Analysis of Mycoardial Time-Activity Curves Related to Radiolabeled Free Fatty Acid Metabolism" in the Cardiology Department at the Free University of Amsterdam, The Netherlands. The traveler also visited the Institute for Clinical and Experimental

Nuclear Medicine in Bonn, West Germany, the Department of Nuclear Medicine in Aachen, West Germany, and the Cyclotron Research Center in Liege, Belgium. He led discussions, reviewed data, and coordinated further collaboration on the preclinical studies and clinical testing of radiopharmaceuticals being developed by the traveler's research group at the Oak Ridge National Laboratory (ORNL).

VISIT TO THE CARDIOLOGY DEPARTMENT, FREE UNIVERSITY HOSPITAL, AMSTERDAM, THE NETHERLANDS

The traveler was invited to serve as an external examiner for the doctoral thesis of Dr. Maichel van Eenige in the Cardiology Department at the Free University Hospital in Amsterdam. The thesis was entitled "Analysis of Myocardial Time-Activity Curves Related to Radiolabeled Free Fatty Acid Metabolism." The thesis committee consisted of seven members, including the traveler and examiners from Zurich, Switzerland, and Grenoble, France, and the chiefs of the departments of nuclear medicine, cardiology, physiology, and medical physics at the Free University. The thesis work of Dr. van Eenige involved detailed analysis and interpretation of the time-activity curves obtained from regions of interest generated from a series of planar gamma camera images of patients following the intravenous administration of iodine-123-labeled fatty acid, 17-iodoheptadecanoic acid (IHA). The IHA is rapidly metabolized with the release of free radioiodide and thus involves a different approach which is not suitable for the prolonged imaging periods required for single photon emission computerized tomography (SPECT).

The thesis approval process is very formal in the Netherlands and involves a public defense of the thesis in the presence of an audience composed of colleagues, friends, and family in front of a panel of university professors (department chairmen) and invited international experts in the field. The thesis completed by Dr. van Eenige for his doctoral degree was an excellent and thorough analysis of the problem associated with mathematical analysis of time-activity curves. His work demonstrated that the analytical techniques used by several investigators for the analysis of externally recorded time-activity curves of patients following injection of iodine-123-labeled IHA are incorrect. While these methods utilize a background correction technique following an injection of iodine-123 sodium iodide followed by a biexponential curve-fitting procedure, Dr. van Eenige clearly showed that this approach gives erroneous values. In contrast, he showed by analysis of both patient data and iterative computer modeling that analysis using a constant and monoexponential curve-fitting gives the best results. The technique which has been developed by Dr. van Eenige will undoubtedly now be widely accepted and should become the standard method used for the analysis of myocardial time-activity curves following administration of straight-chain iodine-123 fatty acids which are rapidly metabolized.

While visiting the Cardiology Department, the traveler also presented a seminar describing studies being conducted by the traveler and his colleagues on the metabolism of the methyl-branched fatty acids developed at ORNL. These studies include the use of an isolated, perfused rat heart system to evaluate the metabolism under carefully controlled conditions. This system allows an evaluation of the flow-independent release of metabolites. In addition, the isolation of sufficient levels of metabolites for chromatographic and chemical analysis can be conducted. This system is being used at ORNL for the isolation of sufficient amounts of the metabolite from radioiodinated 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP). Iodine-123-labeled BMIPP is being used in patients for the SPECT evaluation of regional fatty acid uptake, so it is thus important to have a complete understanding of the metabolism of this agent. In addition to participation on the thesis committee and the opportunity to present and discuss experimental data from ORNL, the traveler also had the opportunity to discuss and coordinate continuing collaborative studies in conjunction with Frans Visser, M.D., and his colleagues. Two cardiology fellows expressed interest in working with the traveler and his colleagues at ORNL, and it is expected that one of the fellows will join the ORNL program in 1990 to work on the metabolism of the radioiodinated fatty acids. During the visit to Amsterdam, the traveler was also invited to visit the University of Grenoble, France, by M. Comet, M.D., chief of the Department of Nuclear Medicine, in conjunction with a future trip.

VISIT TO THE CYCLOTRON RESEARCH CENTER, SART-TILMAN UNIVERSITY, LIEGE, BELGIUM

Following the visit to the Free University, the traveler was invited to visit the Cyclotron Research Center in Liege, Belgium, while in transit to West Germany to discuss and coordinate ongoing collaborative studies and to participate in planning a workshop on clinical applications of the osmium-191/iridium-191m radionuclide generator system developed by the traveler and his colleagues in Liege. Although this workshop was originally planned to be held on October 7 and 8, 1988, prior commitments by several of the key clinical investigators who have performed these studies necessitated rescheduling. The current projection is for the workshop to be held in early 1989. The program will be kept to a small group of investigators who are currently using the generator system or with whom collaborative arrangements have been made. About 15 participants are anticipated (the traveler, colleagues in Liege, and investigators from West Germany, The Netherlands, Belgium, France, and Finland). These discussions are running parallel to the technology transfer activities being conducted by the ORNL Office of Technology Applications, whose goal is to license this technology to a company in the U.S. The U.S. patent has been awarded to the traveler, and the rights have been waived by the Department of Energy to Martin Marietta Energy Systems, Inc.

An important aspect of continuing studies with the osmium-191/iridium-191m generator system involves purification of the reactor-produced osmium-191. In order to maximize the production of osmium-191 in high flux reactors such as the ORNL High Flux Isotope Reactor (HFIR), longer irradiation periods are required with subsequent increased production of the unwanted iridium-192. More importantly, production of osmium-191 in more widely available lower flux reactors requires considerably longer irradiation periods which result in the production of significant levels of iridium-192. At ORNL, the current purification method now involves a distillation of the osmium tetroxide formed by acidification of the processed target material, which is obtained as potassium perosmate. A new microprocessor-controlled solvent extraction method has been developed at Liege which may offer some advantages since the system is completely self-contained and utilizes a radiation sensor at a charcoal trap at the final exit. If radioactivity is detected by the sensor, an electronic valve immediately closes the venting of the system to atmosphere. Since optimizing the scale and size of this process is a major project outlined in the OHER-supported "Radioisotope Production and Development Technology" project, a prototype of this solvent extraction system will be constructed for in-cell use at ORNL.

VISIT TO THE INSTITUTE FOR CLINICAL AND EXPERIMENTAL NUCLEAR MEDICINE UNIVERSITY MEDICAL SCHOOL, BONN, WEST GERMANY

Following discussions with colleagues in Liege, the traveler visited the Institute for Clinical and Experimental Nuclear Medicine at the Friedrich Wilhelms University in Bonn, West Germany. The traveler is leading a variety of collaborative studies which are continuing in conjunction with ORNL and investigators in Bonn. These studies include both clinical and animal investigations with the iodine-123 fatty acids, development of new radiolabeling techniques, and applications of iridium-191m from the osmium-191/iridium-191m radionuclide generator system.

The traveler has been recommended for the prestigious Alexander von Humbolt Award. The von Humbolt Awards are awarded each year to highly qualified scholars of foreign nationality for research projects of their own choice to be conducted at an institution in West Germany. Should the traveler receive this award, he would work in conjunction with institutes in Bonn and Aachen to conduct research in West Germany during the 1991-1992 period.

The traveler also met with the European editors of the journal NucCompact and was invited to serve as one of three members of the new U.S. editorial board. This journal is published in West Germany by GIT Verlag Ernst Giebeler and was established in 1970 as a mechanism for rapid publication of short communications in nuclear medicine and radiopharmaceutical development. It has been listed in "Current Contents" and "Excerpta Medica" since 1983. In order to further

improve the quality of the journal and to stimulate wider authorship, the editorial board has been expanded to the United States.

VISIT TO THE DEPARTMENT OF NUCLEAR MEDICINE AT THE UNIVERSITY OF AACHEN AACHEN, WEST GERMANY

The traveler also visited Sven Reske, M.D., at the University in Aachen to complete drafts of two papers and discuss new collaborative studies which are continuing with new radiolabeling techniques being developed at ORNL. Dr. Reske is continuing patient studies with the iodine-123 fatty acids developed at ORNL and is also involved in research with these agents which focusses on a better understanding of the mechanism of uptake and cellular retention.

SUMMARY AND RECOMMENDATIONS

The traveler had the opportunity to participate in the thesis committee in Amsterdam as a result of his international recognition in the development of fatty acids for applications in nuclear cardiology. Our continued successful interaction with clinical research centers in Europe allows the initiation of clinical testing of several radiopharmaceuticals developed by the traveler at ORNL. More efficient and faster approval for clinical evaluation of new radiopharmaceuticals provides for more effective demonstration of our new developments. These continuing successful collaborative studies clearly illustrate the effectiveness of international collaboration for the initiation of clinical studies and the transfer of new technology developed in the Nuclear Medicine program at ORNL.

ITINERARY

10/1-2/1988	Travel from Oak Ridge, Tennessee, to Amsterdam, The Netherlands
10/3-4/1988	Visit Cardiology Department, Free University Hospital
10/5/1988	Thesis Committee, Cardiology Department, Free University Hospital
10/6-7/1988	Travel from Amsterdam to the Liege, Belgium, visit Cyclotron Research Center
10/7/1988	Visit Cyclotron Research Center, Travel to Bonn, West Germany
10/8-9/1988	Weekend, Bonn, West Germany
10/10/1988	Visit the Institute for Clinical and Experimental Nuclear Medicine, Bonn, West Germany
10/11/1988	Travel from Bonn to Aachen, West Germany, visit the Department of Nuclear Medicine
10/12/1988	Travel from Aachen to Oak Ridge, Tennessee

PERSONS CONTACTED

Amsterdam

C. Duwel, M.D.
J. P. Roos, M.D.
M. van Eenige, Ph.D.
F. Visser, M.D.

Liege

C. Brihaye, Ph.D.
P. Rigo, M.D.

Bonn

H. J. Biersack, M.D.
A. Bockisch, M.D., Ph.D.
P. Oehr, Ph.D.

Aachen

S. N. Reske, M.D.